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During the last two years we have be evaluating the role of the olivary cochlear bundle in some of these effects. We have found that local infusion into the olivary complex of lidocaine, a local anesthetic, leads to an increase in the amplitude of the compound action potential generated by an auditory stimulus recorded at the level of the cochlear nucleus. This suggests that the olivary cochlear bundle tonically inhibits auditory transmission at the level of the hair cells. Conversely, local application of kainate acid, which at very low doses activates cells, leads to a decrease in the compound action potential, consistent with an inhibitory role of the olivary cochlear system. Other drugs, such as pentazozine, that are known to act at the level of the outer hair cells, have opposite effects on the compound action potential in animals with an intact vs. a transected olivary cochlear bundle.

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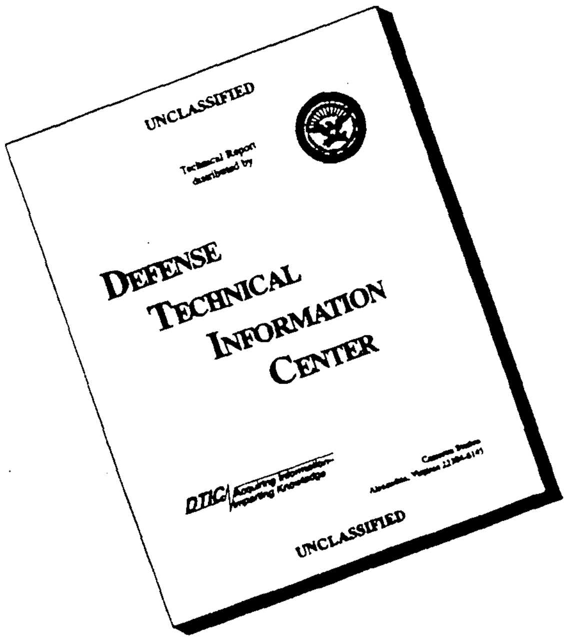

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Jan. 18, 1996
Final Technical Report
Number: F49620-92-J-0300 (the Assert Award)
Title: Cellular Analysis of the Startle Reflex
PI: Michael Davis
Institution: Yale University School of Medicine
34 Park St.
New Haven, Conn. 06508

2. Objectives: No change in objectives

3. Status of effort

In the Assert Award we are interested in how dopamine agonists affect baseline startle amplitude as well as the phenomenon of pre-pulse inhibition. Prior work in our laboratory had found that dopamine agonists such as apomorphine, d-amphetamine or cocaine all increased acoustic startle amplitude. By eliciting startle electrically we deduced that each of these drugs increased startle by acting very early in the acoustic startle pathway (i.e., at or before the cochlear nucleus).

To test this, we have been recording the compound action potential generated by an auditory stimulus at the level of the cochlear nucleus in freely moving rats using a bundle of four previously implanted 25 µm nichrome wires. Each of the dopamine agonists increased the amplitude of the auditory nerve response (N1 component, latency = 0.75 msec). This effect was larger following repeated administration of d-amphetamine on each of 7 days, indicating that it showed sensitization. This suggests that dopamine agonists ultimately can alter processes at the very beginning of the auditory system, which we believe may have considerable relevance for dopamine-induced disruption of auditory prepulse inhibition as well as auditory distractibility and even auditory hallucinations in people. Importantly, all this work has been done in freely moving, awake animals, which has rarely been done when looking at the role of the olivary cochlear bundle.

4. Accomplishments/New Findings

a. Research Highlights

During the last two years we have be evaluating the role of the olivary cochlear bundle in some of these effects. We have found that local infusion into the olivary complex of lidocaine, a local anesthetic, leads to an increase in the amplitude of the compound action potential generated by an auditory stimulus recorded at the level of the cochlear nucleus. This suggests that the olivary cochlear bundle tonically inhibits auditory transmission at the level of the hair cells. Conversely, local application of kainate acid, which at very low doses activates cells, leads to a decrease in the compound action potential, consistent with an inhibitory role of the olivary cochlear system. Other drugs, such as pentazozine, that are known to act at the level of the outer hair cells, have opposite effects on the compound action potential in animals with an intact vs. a transected olivary cochlear bundle.

In other studies, we have found that unilateral lesions of the olivary complex leads to a decrease in the dynamic range of the compound action potential and, most importantly, a large susceptibility to masking, whereby background noise produces a much more substantial decrease in the size of the compound action potential in the lesioned rats vs. the sham lesioned rats. This provides direct evidence in waking animals that the olivary cochlear bundle is involved in facilitating detection of signals in noise, consistent with prior research in anesthetized animals.

b. Significance to the field

A large body of evidence indicates that schizophrenics have significant deficits in their ability to filter out irrelevant sensory stimuli. For example, they are much more distracted by extraneous background noise than are normal controls or other groups of psychiatric patients. Schizophrenics also have a deficit in prepulse inhibition, whereby a weak auditory stimulus normal inhibits the amplitude of the acoustic startle reflex elicited by a loud auditory stimulus presented 50-200 msec later. Interesting, in rats, treatments which increase brain dopamine, thought to be abnormal in schizophrenics, lead to a decrease in prepulse inhibition. Importantly, these disruptive effects are most apparent when the prepulse signal is only a few decibels above the background noise. Hence, it is possible that excess dopamine produced experimentally in rats or naturally in schizophrenia impairs the function of the olivary cochlear system, leading to an inability to detect signals (i.e. the prepulse) in noise. Currently we are testing how treatments that elevate brain dopamine will effect a) prepulse inhibition in noise and quiet and b) the amplitude of the compound action potential elicited by the same prepulse stimulus recorded in noise vs. quiet. The prediction is that dopamine agonists will decrease the amplitude of the compound action potential more in noise than in quiet which should correlate with their greater effectiveness in decreasing prepulse inhibition in noise vs. quiet. Further studies will then try to redo some of these studies after inactivation of the olivary cochlear bundle.

c. Relationship to original goals

Originally, we were interested in determining whether dopamine agonists could ultimately have actions very early on in the auditory system. Our experiments confirmed this. More importantly, we have found in freely moving rats that the olivary cochlear bundle is important for detecting signals in noise and may thus be a major mechanism used for selective attention and sensory gating.

d. Relevance the the AF's research mission

The ability to deal with stress, especially that produced by continuous or intermittent noise, determines in large part performance in a variety of tasks. These could include simple radar detection tasks up to complex on line flight decisions. Understanding the fundamental mechanisms whereby the brain filters out extraneous auditory information, and its inability to do this during high stress or fatigue, could lead to betters methods to improve performance under such conditions.

e. Potential application to AF and civilian technology challenges

Understanding the fundamental mechanisms whereby the brain filters out extraneous auditory information will have direct relevance to certain psychiatric diseases such a schizophrenia. If, in fact, schizophrenics have an abnormal olivary cochlear bundle, this could explain some of their attentional deficits, especially distraction by noise and maybe even auditory hallucinations. Perhaps medications specifically designed to facilitate the function of the olivary cochlear bundle would be uniquely effective in treating this important symptom of schizophrenia.

5. Personnel Supported

Edward Meloni — Graduate Student

6. Publications: None

7. Interactions/Transitions

Enhancement of the compound action potential recorded from the cochlear nucleus of the rat following administration of d-amphetamine and apomorphine. E. G. Meloni & M. Davis. Paper presented at the Society for Neuroscience, Nov. 1994

8. New Inventions or patents - None

9. Honors/Awards

a. Received during this period

Renewal to Michael Davis of Research Scientist Award for years 21-25. National Institute of Mental Health

Renewal to Michael Davis of Merit Award for years 6-10. National Institute of Mental Health

b. Previously received

Phi Beta Kappa, Northwestern University, 1965
Woodrow Wilson Fellow, Yale University, 1965-1966
National Science Foundation Fellow, Yale University, 1966-1969
Sterling Fellow, Yale University, 1968-1969 (Outstanding Graduate Student)
Public Health Service Research Scientist Development Award, Type I,1975-1979
Public Health Service Research Scientist Development Award, Type II, 1980-1984
Public Health Service Research Scientist Award, Level V, 1985-1989
Public Health Service Research Scientist Award, Level V, 1990-1994
Fellow- American Association for the Advancement of Science, 1990
MERIT Award, National Institute of Mental Health, 1991